

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

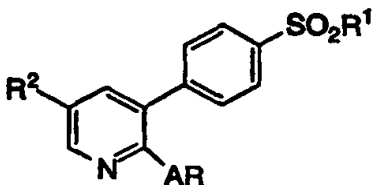
As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 213/74, 401/04, A61K 31/44, 31/55</b>		A1	(11) International Publication Number: <b>WO 99/14195</b>
			(43) International Publication Date: 25 March 1999 (25.03.99)
(21) International Application Number: PCT/CA98/00861 (22) International Filing Date: 11 September 1998 (11.09.98) (30) Priority Data: 60/058,706               12 September 1997 (12.09.97)   US 9800689.3           14 January 1998 (14.01.98)     GB (71) Applicant (for all designated States except US): MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): FRIESEN, Richard [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA). DUBE, Daniel [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA). DESCHENES, Denis [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA). (74) Agent: MURPHY, Kevin, P.; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College, Montreal, Quebec H3A 2Y3 (CA).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report.	
(54) Title: 2-AMINOPYRIDINES AS INHIBITORS OF CYCLOOXYGENASE-2			
(57) Abstract			
The invention encompasses the novel compound of Formula (I) as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula (I). The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula (I).		 <div style="text-align: right;">(I)</div>	

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CJ	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**TITLE OF THE INVENTION****2-AMINOPYRIDINES AS INHIBITORS OF CYCLOOXYGENASE-2****BACKGROUND OF THE INVENTION**

5           This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

          Non-steroidal, antiinflammatory drugs exert most of their antiinflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 (COX-1) or the constitutive enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase, cyclooxygenase-2 (COX-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the COX-1 which has been cloned, sequenced and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, COX-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, COX-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, COX-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of COX-2 will have similar antiinflammatory, antipyretic and analgesic properties to a conventional non-steroidal antiinflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound

10  
15  
20  
25  
30  
35

should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

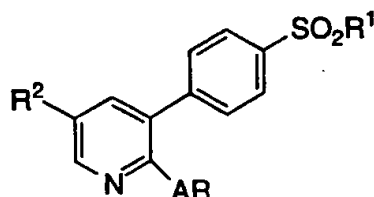
- 5                    Furthermore, such a compound will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's  
10                   disease, for decreasing bone loss particularly in postmenopausal women (i.e. treatment of osteoporosis) and for the treatment of glaucoma.

The potential utilities of selective cyclooxygenase-2 inhibitors are discussed in the following articles:

- 15                   • 1. John Vane, "Towards a better aspirin" in Nature, Vol. 367, pp. 215-216, 1994
- 2. Bruno Battistini, Regina Botting and Y.S. Bakhle, " COX-1 and COX-2: Toward the Development of More Selective NSAIDs" in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.
- 20                   • 3. David B. Reitz and Karen Seibert, "Selective Cyclooxygenase Inhibitors" in Annual Reports in Medicinal Chemistry, James A. Bristol, Editor, Vol. 30, pp. 179-188, 1995.
- 4. Don E. Griswold and Jerry L. Adams, " Constitutive Cyclooxygenase (COX-1) and Inducible Cyclooxygenase (COX-2): Rationale for Selective Inhibition and Progress to Date" in Medicinal  
25                   Research Reviews, Vol. 16, pp. 181-206, 1996.

## SUMMARY OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.

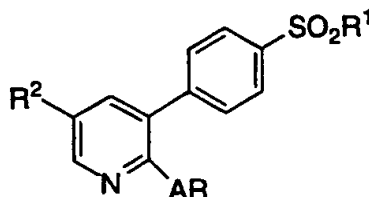


I

The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula I.

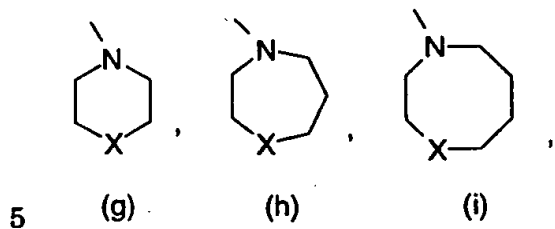
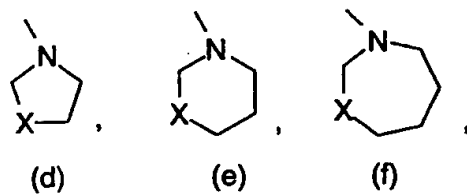
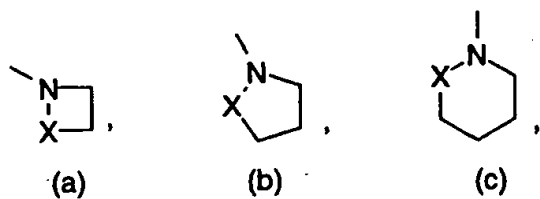
## DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I,



I

-AR is selected from the group consisting of



or a pharmaceutically acceptable salt thereof  
wherein:

- X is selected from the group consisting of
- (a)  $\text{CR}^3\text{R}^4$ ,
  - (b) O,
  - (c) S,
- 5  $\text{R}^1$  is selected from the group consisting of
- (a)  $\text{CH}_3$ ,
  - (b)  $\text{NH}_2$ ,
  - (c)  $\text{NHC(O)CF}_3$ ,
- $\text{R}^2$  is chosen from the group consisting of
- 10 (a) hydrogen
  - (b)  $\text{C}_{1-6}$ alkyl
  - (c)  $\text{C}_{1-6}$ alkoxy,
  - (d)  $\text{C}_{1-6}$ alkylthio,
  - (e)  $\text{C}_{1-6}$ fluoroalkyl,
  - 15 (f)  $\text{C}_{1-6}$ fluoroalkoxy,
  - (g) CN,
  - (h)  $-\text{CO}_2\text{R}^6$ ,
  - (i)  $-\text{C}(\text{R}^7)(\text{R}^8)-\text{OH}$ ,
  - (j)  $-\text{C}_{1-6}\text{alkyl}-\text{CO}_2-\text{R}^9$ ,
  - 20 (k) halo,
  - (l) hydroxy,
  - (m)  $\text{N}_3$ ,
  - (n)  $\text{NO}_2$ ,
  - (o)  $\text{NR}^{10}\text{R}^{11}$ ,
  - 25 (p)  $\text{NHCOR}^{12}$ ,
- $\text{R}^3$  and  $\text{R}^4$  are independently chosen from the group consisting of
- (a) hydrogen,
  - (b)  $\text{C}_{1-6}$ alkyl,
  - (c)  $(\text{CH}_2)_p\text{OR}^5$ ,
  - 30 (d) F,
- or  $\text{R}^3$  and  $\text{R}^4$  are together O,



- $R^5$  is selected from the group consisting of
- (a) hydrogen,
  - (b)  $C_{1-6}$ alkyl,
  - (c)  $C_{1-5}$ acyl,
- 5  $R^6$  to  $R^{12}$  are independently chosen from the group consisting of
- (a) hydrogen
  - (b)  $C_{1-6}$ alkyl, and
- $p$  is 0, 1, 2.
- One preferred embodiment of the invention is that wherein
- 10  $R^1$  is  $CH_3$ .

Another preferred embodiment of the invention is that wherein  $R^2$  is halo or  $C_{1-6}$ fluoroalkyl.

- 15 Another preferred embodiment of the invention is that wherein  $X$  is  $CR^3R^4$ .

In another aspect, the invention also encompasses a pharmaceutical composition for treating an inflammatory disease

20 susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:

a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

In another aspect the invention also encompasses a

25 pharmaceutical composition for treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:

a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

30 In another aspect the invention also encompasses a method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:

administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of formula I and a pharmaceutically acceptable carrier.

5 In another aspect the invention also encompasses a method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:

administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of formula I.

10 In another aspect the invention also encompasses the use of a compound of formula I or a pharmaceutical composition in the manufacture of a medicament for the treatment of an inflammatory disease susceptible to treatment with an a non-steroidal anti-inflammatory agent.

15

The invention is illustrated by the compounds of the Examples disclosed herein as well as the compounds of Table I.

### 1) Definitions

20

The following abbreviations have the indicated meanings:

	AA	=	arachidonic acid
	Ac	=	acetyl
25	AIBN	=	2,2'-azobisisobutyronitrile
	Bn	=	benzyl
	CHO	=	chinese hamster ovary
	CMC	=	1-cyclohexyl-3-(2-morpholinoethyl) carbodiimidemetho- <i>p</i> -toluenesulfonate
30	COX	=	cyclooxygenase
	DBU	=	diazabicyclo[5.4.0]undec-7-ene
	DMAP	=	4-(dimethylamino)pyridine
	DMF	=	N,N-dimethylformamide
	DMSO	=	dimethyl sulfoxide
35	Et <sub>3</sub> N	=	triethylamine

	HBSS	=	Hanks balanced salt solution
	HEPES	=	N-[2-Hydroxyethyl]piperazine-N <sup>1</sup> -[2-ethanesulfonic acid]
	HWB	=	human whole blood
5	IPA	=	isopropyl alcohol
	KHMDS	=	potassium hexamethyldisilazane
	LDA	=	lithium diisopropylamide
	LPS	=	lipopolysaccharide
	mCPBA	=	metachloro perbenzoic acid
10	MMPP	=	magnesium monoperoxyphthalate
	Ms	=	methanesulfonyl = mesyl
	MsO	=	methanesulfonate = mesylate
	NBS	=	N-bromosuccinimide
	NCS	=	N-chlorosuccinimide
15	NIS	=	N-iodosuccinimide
	NSAID	=	non-steroidal anti-inflammatory drug
	ODCB	=	o-dichlorobenzene
	Oxone®	=	potassium peroxymonosulfate
	PCC	=	pyridinium chlorochromate
20	PDC	=	pyridinium dichromate
	r.t.	=	room temperature
	rac.	=	racemic
	Tf	=	trifluoromethanesulfonyl = triflyl
	TFAA	=	trifluoroacetic anhydride
25	TfO	=	trifluoromethanesulfonate = triflate
	THF	=	tetrahydrofuran
	TLC	=	thin layer chromatography
	TMPD	=	N,N,N',N'-tetramethyl-p-phenylenediamine

	Ts	=	p-toluenesulfonyl = tosyl
	TsO	=	p-toluenesulfonate = tosylate
	Tz	=	1H (or 2H)-tetrazol-5-yl
	SO <sub>2</sub> Me	=	methyl sulfone ( also SO <sub>2</sub> CH <sub>3</sub> )
5	SO <sub>2</sub> NH <sub>2</sub>	=	sulfonamide

	<u>Alkyl group abbreviations</u>	<u>Dose Abbreviations</u>
	Me = methyl	bid = bis in die = twice daily
	Et = ethyl	qid = quater in die = four times a day
10	n-Pr = normal propyl	tid = ter in die = three times a day
	i-Pr = isopropyl	
	n-Bu = normal butyl	
	i-Bu = isobutyl	
	s-Bu = secondary butyl	
15	t-Bu = tertiary butyl	
	c-Pr = cyclopropyl	
	c-Bu = cyclobutyl	
	c-Pen = cyclopentyl	
	c-Hex = cyclohexyl	

20

For purposes of this specification "Alkyl" means linear branched and cyclic structures, and combinations thereof, containing the indicated number of carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, 25 hexyl, heptyl, octyl, nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl- 4-propylnonyl, cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1-bicyclo[4.4.0]decyl and the like.

For purposes of this specification "Fluoro alkyl" means 30 alkyl groups, containing the indicated number of carbon atoms, in which one or more hydrogens is replaced by fluorine. Examples are -CF<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>F, -CH<sub>2</sub>CF<sub>3</sub>, c-Pr-F<sub>5</sub>, c-Hex-F<sub>11</sub> and the like.

For purposes of this specification "Alkoxy" means alkoxy groups of the indicated number of carbon atoms of a straight, branched,

or cyclic configuration. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

For purposes of this specification "Alkylthio" means alkylthio groups of the indicated number of carbon atoms of a straight,  
5 branched or cyclic configuration. Examples of alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies -SCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>.

For purposes of this specification "Fluoroalkoxy" means alkoxy groups of the indicated number of carbon atoms of a straight,  
10 branched, or cyclic configuration, in which one or more hydrogens is replaced by fluorine. Examples of fluoroalkoxy alkoxy groups include -OCF<sub>3</sub>, -OCHF<sub>2</sub>, -OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>F, and the like.

For purposes of this specification "halo" means F, Cl, Br, or I.

15 Exemplifying the invention are:

- (1) 3-(4-Methylsulfonyl)phenyl-2-pyrrolidin-1-yl-5-trifluoromethylpyridine,
- (2) 3-(4-Methylsulfonyl)phenyl-2-piperidin-1-yl-5-trifluoromethylpyridine,
- 20 (3) 5-Chloro-3-(4-methylsulfonyl)phenyl-2-piperidin-1-ylpyridine,
- (4) 3-(4-Methylsulfonyl)phenyl-2-piperidin-1-ylpyridine,
- (5) 3-(4-Methylsulfonyl)phenyl-2-(1,2,3,6-tetrahydropyridinyl)-5-trifluoromethylpyridine,
- 25 (6) 2-(Homopiperidin-1-yl)-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine,
- (7) 3-(4-Methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine,
- 30 (8) 3-(4-Methylsulfonyl)phenyl-2-((2R)-2-hydroxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine,
- (9) 5-Chloro-3-(4-methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-ylpyridine,
- (10) 3-(4-Methylsulfonyl)phenyl-2-((2S)-2-methoxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine,
- 35

- (11) 3-(4-Methylsulfonyl)phenyl-2-((2S)-2-acetoxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine,  
(12) 5-Chloro-3-(4-methylsulfonyl)phenyl-2-((2S)-2-methoxymethyl)pyrrolidin-1-ylpyridine,  
5 (13) 3-(4-Methylsulfonyl)phenyl-2-(2-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine,  
(14) (-)-3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine,  
(15) (+)-3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine,  
10 (16) 5-Chloro-3-(4-methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-ylpyridine,  
(17) 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl-3-methyl)piperidin-1-yl-5-trifluoromethylpyridine,  
15 (18) 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)homopiperidin-1-yl-5-trifluoromethylpyridine,  
(19) 3-(4-Methylsulfonyl)phenyl-2-(2-(2-hydroxyethyl))piperidin-1-yl-5-trifluoromethylpyridine,  
(20) 3-(4-Methylsulfonyl)phenyl-2-(4-oxo)piperidin-1-yl-5-trifluoromethylpyridine,  
20 (21) 3-(4-Methylsulfonyl)phenyl-2-(3-oxo)piperidin-1-yl-5-trifluoromethylpyridine,  
(22) 3-(4-Methylsulfonyl)phenyl-2-(4-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine,  
25 (23) 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine,  
(24) 2-(4,4-Difluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine,  
(25) 2-(3,3-Difluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine,  
30 (26) 2-(4-Fluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine,  
(27) 3-(4-Methylsulfonyl)phenyl-2-morpholin-4-yl-5-trifluoromethylpyridine,

(28) 3-(4-Methylsulfonyl)phenyl-2-thiomorpholin-4-yl-5-trifluoromethylpyridine,

5 Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

10 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for  
15 treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

Within this embodiment the invention encompasses  
20 pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula I as described above.

25 In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising:

30 administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

The pharmaceutical compositions of the present invention  
35 comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a

pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from

5 inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts

10 derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-

15 dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like, and basic ion exchange resins.

20 It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic

25 fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns,

30 injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer. Compound I may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in

35 diabetic retinopathy and tumor angiogenesis.



Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, and for the prevention of bone loss (treatment of osteoporosis) and for the treatment of glaucoma.

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), Compound I will prove useful as an alternative to conventional non-steroidal antiinflammatory drugs (NSAID'S) particularly where such non-steroidal antiinflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, Compound I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin; a potentiator including caffeine; an H<sub>2</sub>-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a prostaglandin including misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effective amount of the compound

of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

For the treatment of any of these cyclooxygenase mediated diseases Compound I may be administered orally, topically,  
5 parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-  
10 blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

15 The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any  
20 method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain  
25 the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn  
30 starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a  
35 longer period. For example, a time delay material such as glyceryl

monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard  
5 gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example peanut oil, liquid paraffin,  
10 or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy-  
15 propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example  
20 polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with  
25 partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

30 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth  
35 above, and flavoring agents may be added to provide a palatable oral

preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active  
5 ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

10 The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean,  
15 lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxy-ethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

20 Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension.  
25 This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in  
30 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this  
35 purpose any bland fixed oil may be employed including synthetic mono-

or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions  
5 can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or  
10 suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

Dosage levels of the order of from about 0.01 mg to about 140  
15 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram  
20 of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of  
25 administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from  
30 about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including  
35 the age, body weight, general health, sex, diet, time of administration,

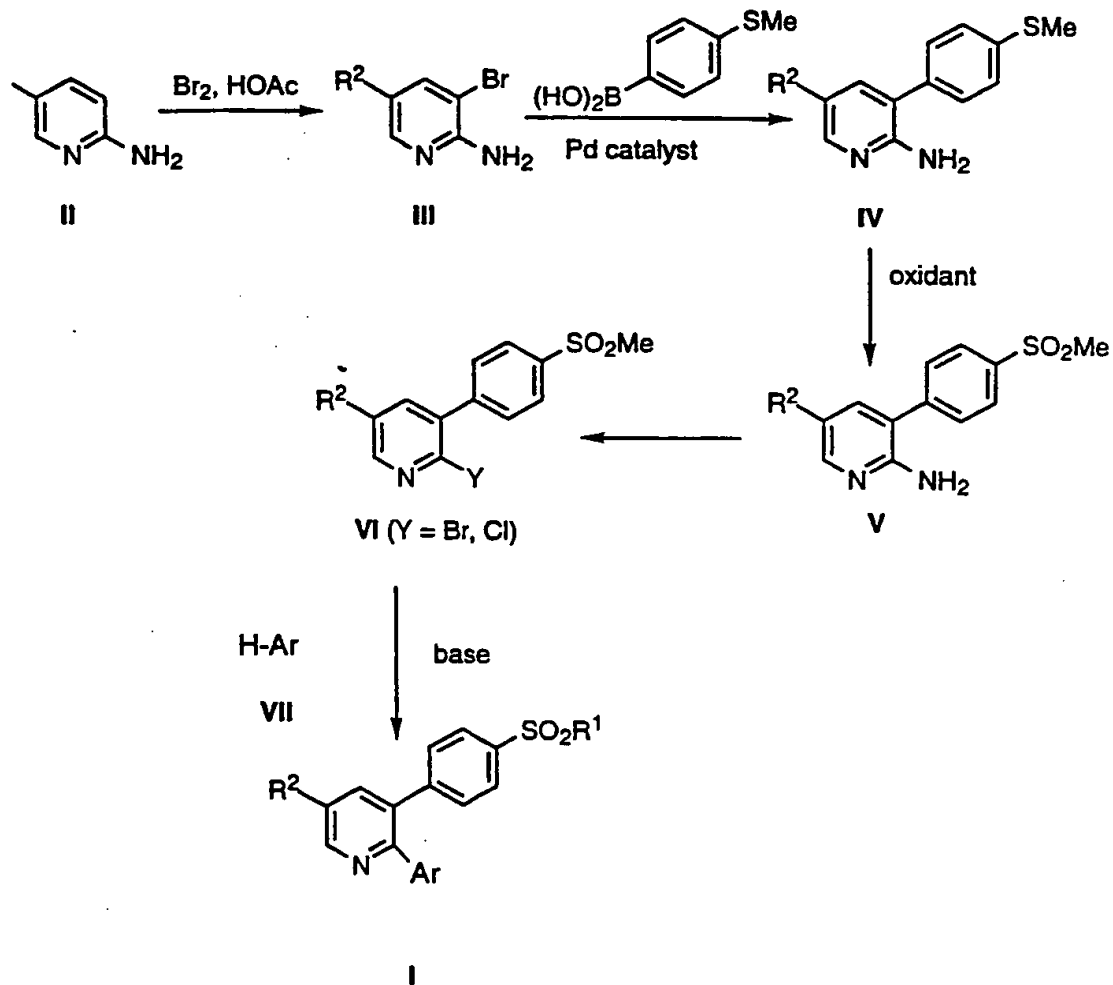
route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

#### Methods of Synthesis

- 5                   The compounds of Formula I of the present invention can be prepared according to the synthetic routes outlined in Scheme 1 and by following the methods described therein.

#### Scheme 1

- 10                   The 2-aminopyridines of Formula I may be prepared in a multi-step sequence from the requisite 2-aminopyridine II. Initial bromination of II with bromine in acetic acid provides the bromide III. A palladium-catalyzed coupling of III with 4-(methylthio)phenylboronic acid in the presence of a suitable base, such as sodium carbonate,
- 15 provides the sulfide IV which can be oxidized using one of several oxidants, such as MMPP, oxone®, or OsO<sub>4</sub>/NMO to the corresponding sulfone V. The amino pyridine V can be converted to the 2-halopyridine VI (X = Br, Cl) by treatment of V with sodium nitrite and either HBr/Br<sub>2</sub> or HCl followed by reaction with POCl<sub>3</sub>. Treatment of VI with an
- 20 appropriately substituted amine VII and a suitable base such as K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub> or KH in an inert solvent such as DMF or DMSO, or alternatively heating a neat mixture of the amine VII and VI in the presence of a copper salt such as CuI, provides the 2-aminopyridine of Formula I.

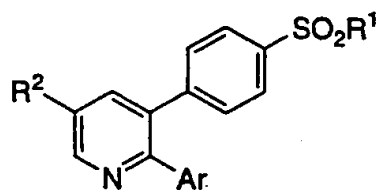
Scheme 1

5

Representative Compounds

10 Tables I illustrates novel compounds of the present invention.

TABLE I



5

<u>Example</u>	<u>R<sup>1</sup></u>	<u>R<sup>2</sup></u>	<u>Ar</u>	
<u>Stereochemistry</u>				
1	Me	CF <sub>3</sub>		-
10				
2	Me	CF <sub>3</sub>		-
3	Me	Cl		-
15				
4	Me	H		-
5	Me	CF <sub>3</sub>		-
6	Me	CF <sub>3</sub>		-
20				



TABLE I (CONTINUED)

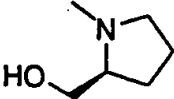
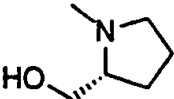
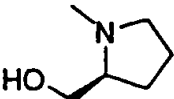
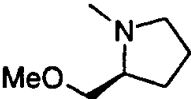
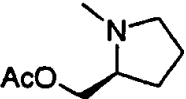
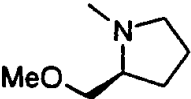
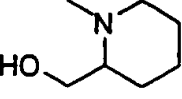
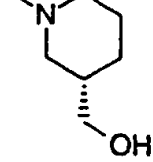
5	7	Me	CF <sub>3</sub>		(S)
	8	Me	CF <sub>3</sub>		(R)
	9	Me	Cl		(S)
	10	Me	CF <sub>3</sub>		(S)
	11	Me	CF <sub>3</sub>		(S)
15	12	Me	Cl		(S)
	13	Me	CF <sub>3</sub>		racemic
	14	Me	CF <sub>3</sub>		(-)-(S)

TABLE I (CONTINUED)

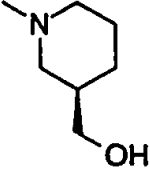
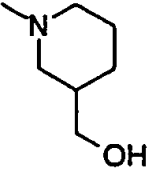
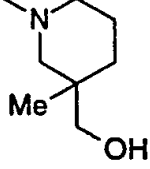
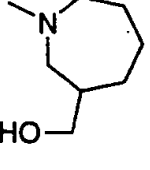
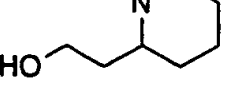
5	15	Me	CF <sub>3</sub>		(+)-(R)
	16	Me	Cl		racemic
	17	Me	CF <sub>3</sub>		racemic
	18	Me	CF <sub>3</sub>		racemic
	19	Me	CF <sub>3</sub>		racemic

TABLE I (CONTINUED)

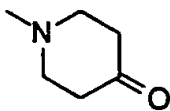
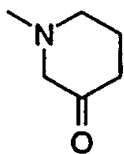
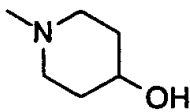
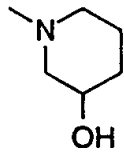
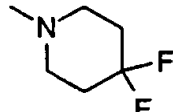
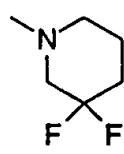
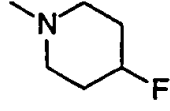
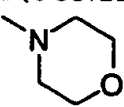
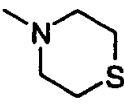
5	20	Me	CF <sub>3</sub>		-
	21	Me	CF <sub>3</sub>		-
	22	Me	CF <sub>3</sub>		-
	23	Me	CF <sub>3</sub>		racemic
	24	Me	CF <sub>3</sub>		-
10	25	Me	CF <sub>3</sub>		-
15	26	Me	CF <sub>3</sub>		-

TABLE I (CONTINUED)

27	Me	CF <sub>3</sub>		-
28	Me	CF <sub>3</sub>		-

5

Assays for determining Biological Activity

The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

INHIBITION OF CYCLOOXYGENASE ACTIVITYWhole cell assays for COX-2 and COX-1 using CHO transfected cell lines

Chinese hamster ovary (CHO) cell lines which have been stably transfected with an eukaryotic expression vector pCDNAIII containing either the human COX-1 or COX-2 cDNA's are used for the assay. These cell lines are referred to as CHO [hCOX-1] and CHO [hCOX-2], respectively. For cyclooxygenase assays, CHO[hCOX-1] cells from suspension cultures and CHO[hCOX-2] cells prepared by trypsinization of adherent cultures are harvested by centrifugation (300 x g, 10 min) and washed once in HBSS containing 15 mM HEPES, pH 7.4, and resuspended in HBSS, 15 mM HEPES, pH 7.4, at a cell concentration of  $1.5 \times 10^6$  cells/ml. Drugs to be tested are dissolved in DMSO to 66.7-fold the highest test drug concentration. Compounds are typically tested at 8 concentrations in duplicate using serial 3-fold serial dilutions in DMSO of the highest drug concentration. Cells ( $0.3 \times 10^6$  cells in 200  $\mu$ l) are preincubated with 3  $\mu$ l of the test drug or DMSO vehicle for 15 min at 37°C. Working solutions of peroxide-free AA (5.5  $\mu$ M and 110  $\mu$ M AA for the CHO [hCOX-1] and CHO [COX-2] assays, respectively) are prepared by a 10-fold dilution of a concentrated AA solution in ethanol into HBSS

containing 15 mM HEPES, pH 7.4. Cells are then challenged in the presence or absence of drug with the AA/HBSS solution to yield a final concentration of 0.5  $\mu$ M AA in the CHO[hCOX-1] assay and a final concentration of 10  $\mu$ M AA in the CHO[hCOX-2] assay. The reaction is  
5 terminated by the addition of 10  $\mu$ l 1 N HCl followed by neutralization with 20  $\mu$ l of 0.5 N NaOH. The samples are centrifuged at 300 x g at 4°C for 10 min, and an aliquot of the clarified supernatant is appropriately diluted for the determination of PGE<sub>2</sub> levels using an enzyme-linked immunoassay for PGE<sub>2</sub> (Correlate PGE<sub>2</sub> enzyme immunoassay kit,  
10 Assay Designs, Inc.). Cyclooxygenase activity in the absence of test compounds is determined as the difference in PGE<sub>2</sub> levels of cells challenged with arachidonic acid versus the PGE<sub>2</sub> levels in cells mock-challenged with ethanol vehicle. Inhibition of PGE<sub>2</sub> synthesis by test compounds is calculated as a percentage of the activity in the presence of  
15 drug versus the activity in the positive control samples.

#### Assay of COX-1 Activity from U937 cell microsomes

U 937 cells are pelleted by centrifugation at 500 x g for 5 min  
20 and washed once with phosphate-buffered saline and repelleted. Cells are resuspended in homogenization buffer consisting of 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA, 2  $\mu$ g/ml leupeptin, 2  $\mu$ g/ml soybean trypsin inhibitor, 2  $\mu$ g/ml aprotinin and 1 mM phenyl methyl sulfonyl fluoride. The cell suspension is sonicated 4 times for 10 sec and is centrifuged at  
25 10,000 x g for 10 min at 4° C. The supernatant is centrifuged at 100,000 x g for 1 hr at 4° C. The 100,000 x g microsomal pellet is resuspended in 0.1 M Tris-HCl, pH 7.4, 10 mM EDTA to approximately 7 mg protein/ml and stored at -80° C.

Microsomal preparations are thawed immediately prior to  
30 use, subjected to a brief sonication, and then diluted to a protein concentration of 125  $\mu$ g/ml in 0.1 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA, 0.5 mM phenol, 1 mM reduced glutathione and 1  $\mu$ M hematin. Assays are performed in duplicate in a final volume of 250  $\mu$ l. Initially, 5  $\mu$ l of DMSO vehicle or drug in DMSO are added to 20  $\mu$ l of 0.1  
35 M Tris-HCl buffer, pH 7.4 containing 10 mM EDTA in wells of a 96-

deepwell polypropylene titre plate. 200 µl of the microsomal preparation are then added and pre-incubated for 15 min at room temperature before addition of 25 µl of 1 M arachidonic acid in 0.1 M Tris-HCl and 10 mM EDTA, pH 7.4. Samples are incubated for 40 min at room temperature and the reaction is stopped by the addition of 25 µl of 1 N HCl. Samples are neutralized with 25 µl of 1 N NaOH prior to quantitation of PGE<sub>2</sub> content by radioimmunoassay (Dupont-NEN or Amersham assay kits). Cyclooxygenase activity is defined as the difference between PGE<sub>2</sub> levels in samples incubated in the presence of arachidonic acid and ethanol vehicle.

#### Assay of the activity of purified human COX-2

The enzyme activity is measured using a chromogenic assay based on the oxidation of N,N,N',N'-tetramethyl-p-phenylenediamine (TMPD) during the reduction of PGG<sub>2</sub> to PGH<sub>2</sub> by COX-2 (Copeland et al. (1994) Proc. Natl. Acad. Sci. 91, 11202-11206).

Recombinant human COX-2 is purified from Sf9 cells as previously described (Percival et al (1994) Arch. Biochem. Biophys. 15, 111-118). The assay mixture (180 µL) contains 100 mM sodium phosphate, pH 6.5, 2 mM genapol X-100, 1 µM hematin, 1 mg/ml gelatin, 80-100 units of purified enzyme (One unit of enzyme is defined as the amount of enzyme required to produce an O.D. change of 0.001/min at 610 nm) and 4 µL of the test compound in DMSO. The mixture is pre-incubated at room temperature (22°C) for 15 minutes prior to initiation of the enzymatic reaction by the addition of 20 µL of a sonicated solution of 1 mM arachidonic acid (AA) and 1 mM TMPD in assay buffer (without enzyme or hematin). The enzymatic activity is measured by estimation of the initial velocity of TMPD oxidation over the first 36 sec of the reaction. A non-specific rate of oxidation is observed in the absence of enzyme (0.007 - 0.010 O.D. /min) and is subtracted before the calculation of the % inhibition. IC<sub>50</sub> values are derived from 4-parameter least squares non-linear regression analysis of the log-dose vs % inhibition plot.

#### HUMAN WHOLE BLOOD ASSAY

### Rationale

Human whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective COX-2 inhibitors. Studies have shown that normal human blood does not contain the COX-2 enzyme. This is consistent with the observation that COX-2 inhibitors have no effect on PGE<sub>2</sub> production in normal blood. These inhibitors are active only after incubation of human whole blood with LPS, which induces COX-2. This assay can be used to evaluate the inhibitory effect of selective COX-2 inhibitors on PGE<sub>2</sub> production. As well, platelets in whole blood contain a large amount of the COX-1 enzyme. Immediately following blood clotting, platelets are activated through a thrombin-mediated mechanism. This reaction results in the production of thromboxane B<sub>2</sub> (TxB<sub>2</sub>) via activation of COX-1. Thus, the effect of test compounds on TxB<sub>2</sub> levels following blood clotting can be examined and used as an index for COX-1 activity. Therefore, the degree of selectivity by the test compound can be determined by measuring the levels of PGE<sub>2</sub> after LPS induction (COX-2) and TxB<sub>2</sub> following blood clotting (COX-1) in the same assay.

### Method

#### A. COX-2 (LPS-induced PGE<sub>2</sub> production)

Fresh blood is collected in heparinized tubes by venipuncture from both male and female volunteers. The subjects have no apparent inflammatory conditions and have not taken any NSAIDs for at least 7 days prior to blood collection. Plasma is immediately obtained from a 2mL blood aliquot to use as blank (basal levels of PGE<sub>2</sub>). The remaining blood is incubated with LPS (100 µg/ml final concentration, Sigma Chem, #L-2630 from E. coli; diluted in 0.1% BSA (Phosphate buffered saline) for 5 minutes at room temperature. Five hundred µL aliquots of blood are incubated with either 2µL of vehicle (DMSO) or 2µL of a test compound at final concentrations varying from 10nM to 30µM for 24 hours at 37°C. At the end of the incubation, the blood is centrifuged at 12,000 x g for 5 minutes to obtain plasma. A 100µL

aliquot of plasma is mixed with 400 $\mu$ L of methanol for protein precipitation. The supernatant is obtained and is assayed for PGE<sub>2</sub> using a radioimmunoassay kit (Amersham, RPA#530) after conversion of PGE<sub>2</sub> to its methyl oximate derivative according to the manufacturer's procedure.

#### B. COX-1 (Clotting-induced TxB<sub>2</sub> production)

Fresh blood is collected into vacutainers containing no anticoagulants. Aliquots of 500 $\mu$ L are immediately transferred to siliconized microcentrifuge tubes preloaded with 2 $\mu$ L of either DMSO or a test compound at final concentrations varying from 10nM to 30 $\mu$ M. The tubes are vortexed and incubated at 37°C for 1 hour to allow blood to clot. At the end of incubation, serum is obtained by centrifugation (12,000 x g for 5 min.). A 100 $\mu$ L aliquot of serum is mixed with 400 $\mu$ L of methanol for protein precipitation. The supernatant is obtained and is assayed for TxB<sub>2</sub> using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

#### RAT PAW EDEMA ASSAY

##### Protocol

Male Sprague-Dawley rats (150-200 g) are fasted overnight and are given, po, either vehicle (1% methocel or 5% Tween 80) or a test compound. One hr later, a line is drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V<sub>0</sub>) is measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals are then injected subplantarly with 50 ml of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e. 500 mg carrageenan per paw). Three hr later, the paw volume (V<sub>3</sub>) is measured and the increases in paw volume (V<sub>3</sub> - V<sub>0</sub>) are calculated. The animals are sacrificed by CO<sub>2</sub> asphyxiation and the absence or presence of stomach lesions scored. Data is compared with the vehicle-



control values and percent inhibition calculated. All treatment groups are coded to eliminate observer bias.

#### LPS-Induced Pyrexia in Conscious Rats

5

Male Sprague-Dawley rats (150 - 200 g) were fasted for 16 - 18 h before use. At approximately 9:30 a.m., the animals were placed temporarily in plexiglass restrainers and their baseline rectal temperature was recorded using a flexible temperature probe (YSI series 400) connected to a digital thermometer (Model 08502, Cole Parmer). The same probe and thermometer were used for all animals to reduce experimental error. The animals were returned to their cages after the temperature measurements. At time zero, the rats were injected intraperitoneally with either saline or LPS (2 mg/kg, Sigma Chem) and the rectal temperature was remeasured at 5, 6 and 7 h following LPS injection. After the measurement at 5 h, when the increase in temperature had reached a plateau, the LPS-injected rats were given either the vehicle (1% methocel) or a test compound orally to determine whether the compound could reverse the pyrexia. Percent reversal of the pyrexia was calculated using the rectal temperature obtained at 7 h in the control (vehicle-treated) group as the reference (zero reversal) point. Complete reversal of pyrexia to the pre-LPS baseline value is taken as 100%.

#### LPS-Induced Pyrexia in Conscious Squirrel Monkeys

Temperature probes were surgically implanted under the abdominal skin in a group of squirrel monkeys (*Saimiri sciureus*) (1.0 - 1.7 kg). This allows for the monitoring of body temperature in conscious, unrestrained monkeys by a telemetric sensing system (Data Sciences International, Minnesota). The animals were fasted and were placed in individual cages for acclimatization 13 - 14 h before use. Electronic receivers were installed on the side of the cages which pick up signals from the implanted temperature probes. At approximately 9:00 a.m. on the day of the experiment, the monkeys were restrained temporarily in training chairs and were given a bolus I.V. injection of LPS, (6

mg/kg, dissolved in sterile saline). The animals were returned to their cages and body temperature was recorded continuously every 5 min. Two h after injection of LPS, when the body temperature had increased by 1.5 - 2°C, the monkeys were dosed orally with either vehicle (1% methocel) or a test compound (3 mg/kg). One hundred minutes later, the difference between the body temperature and the baseline value was determined. Percent inhibition was calculated taking the value in the control group as 0% inhibition.

10 Acute Inflammatory Hyperalgesia Induced by Carrageenan in Rats

Experiments were performed using male Sprague Dawley rats (90-110g). Hyperalgesia to mechanical compression of the hind paw was induced by intraplantar injection of carrageenan (4.5 mg into one hind paw) 3 h previously. Control animals received an equivalent volume of saline (0.15 ml intraplantar). A test compound (0.3-30 mg/kg, suspended in 0.5% methocel in distilled water) or vehicle (0.5% methocel) was administered orally (2ml/kg) 2 h after carrageenan. The vocalisation response to compression of the hind paw was measured 1 h later using a Ugo Basile algesiometer.

Statistical analysis for carrageenan-induced hyperalgesia was performed using one-way ANOVA (BMDP Statistical Software Inc.). Hyperalgesia was determined by subtracting the vocalisation threshold in saline injected rats from that obtained in animals injected with carrageenan. Hyperalgesia scores for drug-treated rats were expressed as a percentage of this response. ID<sub>50</sub> values (the dose producing 50% of the maximum observed response) were then calculated by nonlinear least squares regression analysis of mean data using GraFit (Erithacus Software).

Adjuvant-Induced Arthritis in Rats

Seventy, 6.5-7.5 week old, female Lewis rats (body weight ~146-170 g) were weighed, ear marked, and assigned to groups (a negative control group in which arthritis was not induced, a vehicle

control group, a positive control group administered indomethacin at a total daily dose of 1 mg/kg and four groups administered with a test compound at total daily doses of 0.10-3.0 mg/kg) such that the body weights were equivalent within each group. Six groups of 10 rats each were injected into a hind paw with 0.5 mg of *Mycobacterium butyricum* in 0.1 ml of light mineral oil (adjuvant), and a negative control group of 10 rats was not injected with adjuvant. Body weights, contralateral paw volumes (determined by mercury displacement plethysmography) and lateral radiographs (obtained under Ketamine and Xylazine anesthesia) were determined before (day -1) and 21 days following adjuvant injection, and primary paw volumes were determined before (day -1) and on days 4 and 21 following adjuvant injection. The rats were anesthetized with an intramuscular injection of 0.03 - 0.1 ml of a combination of Ketamine (87 mg/kg) and Xylazine (13 mg/kg) for radiographs and injection of adjuvant. The radiographs were made of both hind paws on day 0 and day 21 using the Faxitron (45 kVp, 30 seconds) and Kodak X-OMAT TL film, and were developed in an automatic processor. Radiographs were evaluated for changes in the soft and hard tissues by an investigator who was blinded to experimental treatment. The following radiographic changes were graded numerically according to severity: increased soft issue volume (0-4), narrowing or widening of joint spaces (0-5) subchondral erosion (0-3), periosteal reaction (0-4), osteolysis (0-4) subluxation (0-3), and degenerative joint changes (0-3). Specific criteria were used to establish the numerical grade of severity for each radiographic change. The maximum possible score per foot was 26. A test compound at total daily doses of 0.1, 0.3, 1, and 3 mg/kg/day, Indomethacin at a total daily dose of 1 mg/kg/day, or vehicle (0.5% methocel in sterile water) were administered per os b.i.d. beginning post injection of adjuvant and continuing for 21 days. The compounds were prepared weekly, refrigerated in the dark until used, and vortex mixed immediately prior to administration.

Two-factor ('treatment' and 'time') analysis of variance with repeated measures on 'time' were applied to the % changes for body weight and foot volumes and to the rank-transformed radiographic total scores. A *post hoc* Dunnett's test was conducted to compare the effect of

treatments to vehicle. A one-way analysis of variance was applied to the thymic and spleen weights followed by the Dunnett's test to compare the effect of treatments to vehicle. Dose-response curves for % inhibition in foot volumes on days 4, 14 and 21 were fitted by a 4-parameter logistic function using a nonlinear least squares' regression. ID<sub>50</sub> was defined as the dose corresponding to a 50% reduction from the vehicle and was derived by interpolation from the fitted 4-parameter equation.

## PHARMACOKINETICS IN RATS

### Per Os Pharmacokinetics in Rats

#### PROCEDURE:

The animals are housed, fed and cared for according to the Guidelines of the Canadian Council on Animal Care.

Male Sprague Dawley rats (325-375 g) are fasted overnight prior to each PO blood level study.

The rats are placed in the restrainer one at a time and the box firmly secured. The zero blood sample is obtained by nicking a small (1 mm or less) piece off the tip of the tail. The tail is then stroked with a firm but gentle motion from the top to the bottom to milk out the blood. Approximately 1 mL of blood is collected into a heparinized vacutainer tube.

Compounds are prepared as required, in a standard dosing volume of 10mL/kg, and administered orally by passing a 16 gauge, 3" gavaging needle into the stomach.

Subsequent bleeds are taken in the same manner as the zero bleed except that there is no need to nick the tail again. The tail is cleaned with a piece of gauze and milked/stroked as described above into the appropriately labelled tubes.

Immediately after sampling, blood is centrifuged, separated, put into clearly marked vials and stored in a freezer until analysed.

Typical time points for determination of rat blood levels after PO dosing are:

0, 15min, 30min, 1h, 2h, 4h, 6h

- 5 After the 4 hr time point bleed, food is provided to the rats *ad libitum*. Water is provided at all times during the study.

Vehicles:

- 10 The following vehicles may be used in PO rat blood level determinations:

PEG 200/300/400: restricted to 2 mL/kg

Methocel 0.5% - 1.0%: 10mL/kg

Tween 80: 10mL/kg

15

Compounds for PO blood levels can be in suspension form. For better dissolution, the solution can be placed in a sonicator for approximately 5 minutes.

- 20 For analysis, aliquots are diluted with an equal volume of acetonitrile and centrifuged to remove protein precipitate. The supernatant is injected directly onto a C-18 HPLC column with UV detection. Quantitation is done relative to a clean blood sample spiked with a known quantity of drug. Bioavailability (F) is assessed by comparing  
25 area under the curve (AUC) i.v. versus p.o.

$$F = \frac{AUC_{po}}{AUC_{iv}} \times \frac{DOSE_{iv}}{DOSE_{po}} \times 100\%$$

30

Clearance rates are calculated from the following relation:

$$CL = \frac{DOSE_{iv}(mg/kg)}{AUC_{iv}}$$

35

The units of CL are mL/h•kg (milliliters per hour kilogram)

Intravenous Pharmacokinetics in Rats

**PROCEDURE:**

The animals are housed, fed and cared for according to the Guidelines of the Canadian Council on Animal Care.

5

Male Sprague Dawley (325-375 g) rats are placed in plastic shoe box cages with a suspended floor, cage top, water bottle and food.

10

The compound is prepared as required, in a standard dosing volume of 1 mL/kg.

15

Rats are bled for the zero blood sample and dosed under CO<sub>2</sub> sedation. The rats, one at a time, are placed in a primed CO<sub>2</sub> chamber and taken out as soon as they have lost their righting reflex. The rat is then placed on a restraining board, a nose cone with CO<sub>2</sub> delivery is placed over the muzzle and the rat restrained to the board with elastics. With the use of forceps and scissors, the jugular vein is exposed and the zero sample taken, followed by a measured dose of compound which is injected into the jugular vein. Light digital pressure is applied to the injection site, and the nose cone is removed. The time is noted. This constitutes the zero time point.

25

The 5 min bleed is taken by nicking a piece (1-2 mm) off the tip of the tail. The tail is then stroked with a firm but gentle motion from the top of the tail to the bottom to milk the blood out of the tail. Approximately 1 mL of blood is collected into a heparinized collection vial. Subsequent bleeds are taken in the same fashion, except that there is no need to nick the tail again. The tail is cleaned with a piece of gauze and bled, as described above, into the appropriate labelled tubes.

30

Typical time points for determination of rat blood levels after I.V. dosing are either:

0, 5 min, 15min, 30min, 1h, 2h, 6h  
or  
0, 5 min, 30min, 1h, 2h, 4h, 6h.

35

Vehicles:

The following vehicles may be used in IV rat blood level determinations:

- 5    Dextrose:                    1mL/kg  
      Moleculsol 25%:        1mL/kg  
      DMSO (dimethylsulfoxide): Restricted to a dose volume of 0.1 mL per  
   animal  
      PEG 200:                    Not more than 60% mixed with 40% sterile  
10                                    water - 1mL/kg

With Dextrose, either sodium bicarbonate or sodium carbonate can be added if the solution is cloudy.

- 15   For analysis, aliquots are diluted with an equal volume of acetonitrile and centrifuged to remove protein precipitate. The supernatant is injected directly onto a C-18 HPLC column with UV detection. Quantitation is done relative to a clean blood sample spiked with a known quantity of drug. Bioavailability (F) is assessed by comparing  
20   area under the curve (AUC) i.v. versus p.o.

$$F = \frac{AUC_{po}}{AUC_{iv}} \times \frac{DOSE_{iv}}{DOSE_{po}} \times 100\%$$

- 25   Clearance rates are calculated from the following relation:

$$CL = \frac{DOSE_{iv}(mg/kg)}{AUC_{iv}}$$

- 30   The units of CL are mL/h•kg (milliliters per hour kilogram)

NSAID-INDUCED GASTROPATHY IN RATS

35   Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of Cox-1 in the gastrointestinal tract. Rats are particularly

sensitive to the actions of NSAIDs. In fact, rat models have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring fecal  $^{51}\text{Cr}$  excretion after systemic injection of  $^{51}\text{Cr}$ -labeled red blood cells. Fecal  $^{51}\text{Cr}$  excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

#### Methods

Male Sprague Dawley rats (150 - 200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats are injected via a tail vein with 0.5 mL of  $^{51}\text{Cr}$ -labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water *ad lib*. Feces are collected for a 48 h period and  $^{51}\text{Cr}$  fecal excretion is calculated as a percent of total injected dose.  $^{51}\text{Cr}$ -labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400 Ci of sodium  $^{51}\text{Cr}$ chromate for 30 min. at 37C. At the end of the incubation, the red blood cells are washed twice with 20 mL HBSS to remove free sodium  $^{51}\text{Cr}$ chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20 Ci) is injected per rat.

#### PROTEIN-LOSING GASTROPATHY IN SQUIRREL MONKEYS

##### Rationale

Protein-losing gastropathy (manifested as appearance of circulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard non-steroidal anti-inflammatory drugs (NSAIDs). This can be quantitatively assessed by intravenous administration of  $^{51}\text{CrCl}_3$  solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum.



Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.

5 Methods

Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocel or 5% Tween 80 in H<sub>2</sub>O vehicles, (3mL/kg b.i.d.) or test compounds at doses from 1 - 100 mg/kg b.i.d. for 5 days. Intravenous <sup>51</sup>Cr (5Ci/kg in 1 ml/kg phosphate buffer saline (PBS)) is administered 1 h after the last drug/vehicle dose, and feces collected for 24 h in a metabolism cage and assessed for excreted <sup>51</sup>Cr by gamma-counting. Venous blood is sampled 1 h and 8 h after the last drug dose, and plasma concentrations of drug measured by RP-HPLC.

15 Representative Biological Data

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined by measuring the amount of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a putative inhibitor. The IC<sub>50</sub> values represent the concentration of putative inhibitor required to return PGE<sub>2</sub> synthesis to 50% of that obtained as compared to the uninhibited control.

The results for certain of the biological assays may be seen in Table II.

TABLE II

<u>Example</u>	<u>COX-2 (IC<sub>50</sub> mM)</u>		<u>COX-1 (IC<sub>50</sub> mM)</u>	
	<u>CHO</u>	<u>HWB</u>	<u>U-937</u>	<u>HWB</u>
5				
1	0.02	9.7	>10	-
2	0.004	0.3	3	>100
3	0.002	0.2	1-3	-
4	0.13	6.0	>50	-
10 5	0.002	1.0	1-3	-
6	0.004	6.0	10	-
7	0.04	0.2	3-10	-
8	>5	>33	>10	-
9	0.03	0.1	1-3	-
15 10	0.09	3.1	3-10	-
11	0.07	<0.4	>10	-
12	0.01	5.3	3-10	-
13	0.10	2.7	10	-
14	0.03	0.5	3-10	-
20 15	0.03	26.6	>10	-
16	0.24	0.7	>10	-
17	0.40	5.3	>10	-
18	0.08	23.4	>10	-
19	0.92	3.2	>10	-
25 20	0.09	10.4	>10	-
21	0.11	5.3	>10	-
22	0.03	10.8	>10	-
23	0.03	7.5	>10	-
24	0.02	10.3	>10	-
30 25	0.08	4.7	>10	-
26	0.01	1.7	3-10	-
27	0.06	3.6	>10	-
28	0.03	1.4	3-10	-

35

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

- 5 (i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;
- (ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C;
- 10 (iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only;
- (iv) melting points are uncorrected and 'd' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;
- 15 (v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;
- 20 (vi) yields are given for illustration only;
- (vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;
- 25 (viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)), r.t.(room temperature), h (hour(s)), min (minute(s)).
- 30
- 35

## EXAMPLE 1

3-(4-Methylsulfonyl)phenyl-2-pyrrolidin-1-yl-5-trifluoromethylpyridine5 Step 1: 2-Amino-3-bromo-5-trifluoromethylpyridine

To a solution of 2-amino-5-trifluoromethylpyridine (9 g) in acetic acid (75 mL) at r.t. was added bromine (5.8 mL) slowly. After 1 h, the acid was neutralized by the careful addition of sodium hydroxide (10 N) at 0°C. The resulting orange precipitate was dissolved in ether and  
10 washed successively with saturated potassium carbonate, saturated Na<sub>2</sub>SO<sub>3</sub> and brine, dried and concentrated. The residual solid was stirred vigorously in hexane for 1 h to provide, after filtration, the title compound as a white solid (10.2 g).

15 Step 2: 2-Amino-3-(4-methylthio)phenyl-5-trifluoromethylpyridine

A mixture of the bromide from Step 1, 4-methylthiobenzene boronic acid (Li, et. al. *J. Med. Chem.* 1995, 38, 4570) (8.5 g), 2M aqueous sodium carbonate (60 mL) and palladium tetrakis(triphenylphosphine) (490 mg) in ethanol/benzene (100 mL, 1:1) was heated at reflux for 15 h.  
20 The mixture was cooled to r.t., diluted with water and extracted with ether. The organics were concentrated and the residue was subjected to stirred vigorously in ether/hexane for 1 h to provide, after filtration, the title compound (11.2 g) as a beige solid.

25 Step 3: 2-Amino-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine

A mixture of 2-amino-3-(4-methylthio)phenyl-5-trifluoromethylpyridine (9.7 g), OsO<sub>4</sub> (2 mL of a 4% solution in water) and NMO (13 g) in acetone/water (60 mL:5 mL) was stirred at r.t. overnight.  
30 Saturated aqueous Na<sub>2</sub>SO<sub>3</sub> was then added and the resulting mixture was stirred for 30 min. The acetone was evaporated and the resulting mixture was extracted with ether and ethyl acetate. The combined organics were washed with Na<sub>2</sub>SO<sub>3</sub>, water, brine and then concentrated. The solid residue was stirred vigorously in hexane and

ether for 1 h and then filtered to provide the title compound as a pale yellow solid (9.9 g).

Step 4: 2-Bromo-3-(4-methylsulfonyl)phenyl-5-trifluoromethyl-pyridine

5  
To a solution of 2-amino-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (7.2 g) in 48% HBr (25 mL) and bromine (3.5 mL) at 0°C was carefully and slowly added sodium nitrite (3.9 g). The mixture was warmed to r.t. and stirred for 4 h. The mixture was treated  
10 with saturated sodium carbonate and extracted with ether. The organics were washed successively with saturated sodium bisulfite and brine, dried and concentrated. Flash chromatography (7:3 hexane/ethyl acetate) of the residue provided the title compound as a pale yellow solid (6.4 g).

15  
Step 5: 3-(4-Methylsulfonyl)phenyl-2-pyrrolidin-1-yl-5-trifluoromethylpyridine

A mixture of pyrrolidine (0.5 mL), potassium carbonate (250  
20 mg) and 2-bromo-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (150 mg) in DMSO (5 mL) was stirred at 65°C until tlc analysis indicated completion of the reaction (15 h). To the mixture was added 1 N HCl and the mixture was extracted with ethyl acetate. The organics were washed with saturated sodium bicarbonate and brine, dried (MgSO<sub>4</sub>)  
25 and concentrated. Flash chromatography (1:1 hexane/ethyl acetate) or stirring the residual material vigorously in a suitable solvent (such as ether or ethyl acetate) provided the title compound as a white solid (93 mg), m.p. 184-187°C.

## EXAMPLE 2

3-(4-Methylsulfonyl)phenyl-2-piperidin-1-yl-5-trifluoromethylpyridine

Following the procedures described in Example 1, Step 5,  
5 but substituting piperidine for pyrrolidine, the title compound was  
obtained as a pale yellow solid, m.p. 159-160°C.

## EXAMPLE 3

10 5-Chloro-3-(4-methylsulfonyl)phenyl-2-piperidin-1-ylpyridineStep 1: 2-Amino-3-bromo-5-chloropyridine

To a solution of 2-amino-5-chloropyridine (10 g) in acetic  
acid (75 mL) at r.t. was added bromine (2.6 mL) slowly. After 30 min, the  
15 acid was neutralized by the careful addition of sodium hydroxide (10 N)  
at 0°C. The resulting orange precipitate was dissolved in ethyl acetate  
and washed successively with saturated potassium carbonate, saturated  
Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and brine, dried and concentrated. Flash chromatography  
(eluting with hexane/ethyl acetate, 3:1 v/v) of the residual solid provided  
20 the title compound as a pale yellow solid (14.8 g).

Step 2: 2-Amino-5-chloro-3-(4-methylsulfonyl)phenylpyridine

Following the procedures described in Example 1, Steps 2  
and 3, but substituting 2-amino-3-bromo-5-chloropyridine from Step 1 (5  
25 g) for 2-amino-3-bromo-5-trifluoromethylpyridine, the title compound  
was obtained as a white solid (5.3 g).

Step 3: 2,5-Dichloro-3-(4-methylsulfonyl)phenylpyridine

To a solution of 2-amino-5-chloro-3-(4-  
30 methylsulfonyl)phenylpyridine (1.5 g) in dioxane/water (15 mL) and  
concentrated HCl (1.5 mL) at 0°C was added a solution of sodium nitrite  
(580 mg) in 1.5 mL water. The mixture was stirred at 5°C for 1 h and  
then 10 N NaOH was added until the pH was basic. The mixture was  
diluted with water and extracted four times with ether. The combined  
35 organics were washed with 10% NaOH, dried and concentrated. The

crude solid (1.4 g) and POCl<sub>3</sub> (3 L) was heated at 110°C for 3 h in a steel bomb. The mixture was cooled to r.t., diluted carefully with water and neutralized with 10 N NaOH. The mixture was extracted with ether and the organics were washed with brine, dried and concentrated. The solid  
5 material was recrystallized from toluene to provide the title compound as an off-white solid (1.2 g).

Step 4: 5-Chloro-3-(4-methylsulfonyl)phenyl-2-piperidin-1-ylpyridine

10 A mixture of piperidine (250 mg), cesium carbonate (680 mg) and 2,5-dichloro-3-(4-methylsulfonyl)phenylpyridine (240 mg) in DMSO (3 mL) was stirred at 120°C until tlc analysis indicated completion of the reaction (15 h). To the mixture was added water and the mixture was extracted with ethyl acetate. The organics were washed with brine,  
15 dried (MgSO<sub>4</sub>) and concentrated. Chromatography (1:1 hexane/ethyl acetate) of the residual material provided the title compound as a white solid (101 mg), m.p. 184-187°C.

Elemental Analysis: Calculated: C, 58.20; H, 5.46; N, 7.98  
Found: C, 58.06; H, 5.60; N, 7.85

20

EXAMPLE 4

3-(4-Methylsulfonyl)phenyl-2-piperidin-1-ylpyridine

25 Step 1: 2-Chloro-3-(4-methylthio)phenylpyridine

To a solution of 2-chloro-3-hydroxypyridine (2 g) and triethylamine (5 mL) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) at -78°C was added trifluoromethanesulfonic anhydride (2.8 mL) and was then warmed to r.t.. Saturated ammonium chloride was added and the mixture was  
30 extracted with ether. The organics were washed with water and brine, dried and concentrated. The residual material containing the crude triflate, 4-methylthiobenzene boronic acid (Li, et. al. *J. Med. Chem.* 1995, 38, 4570) (2.6 g), 2M aqueous sodium carbonate (17 mL) and catalytic palladium tetrakis(triphenylphosphine) in ethanol/benzene (40 mL, 1:1)

was heated at reflux for 3 h. The mixture was cooled to r.t., diluted with water and extracted with ether. The organics were concentrated and the residue was subjected to flash chromatography (85:15 hexane/ethyl acetate). The title compound was obtained as a solid (640 mg).

5

Step 2: 2-Chloro-3-(4-methylsulfonyl)phenylpyridine

Following the procedures described in Example 1, Step 3, but substituting 2-chloro-3-(4-methylthio)phenylpyridine from Step 1 for 2-amino-3-(4-methylthio)phenyl-5-trifluoromethylpyridine, the title compound was obtained as a white solid.

10

Step 3: 3-(4-Methylsulfonyl)phenyl-2-piperidin-1-ylpyridine

A mixture of piperidine (0.5 mL), potassium carbonate (100 mg) and 2-chloro-3-(4-methylthio)phenylpyridine (150 mg) in DMSO (1.5 mL) was stirred at 165°C until tlc analysis indicated completion of the reaction (15 h). Water was added and the mixture was extracted with ether. The organics were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (7:3 hexane/ethyl acetate) provided the title compound as a yellow solid (80 mg).

15

Elemental Analysis: Calculated: C, 64.53; H, 6.37; N, 8.85  
Found: C, 64.71; H, 6.40; N, 8.47

20

### EXAMPLE 5

25 3-(4-Methylsulfonyl)phenyl-2-(1,2,3,6-tetrahydropyridinyl)-5-trifluoromethylpyridine

Following the procedures described in Example 1, Step 5, but substituting 1,2,3,6-tetrahydropyridine for pyrrolidine, the title compound was obtained as a solid, m.p. 149-149.5°C.

30



## EXAMPLE 6

2-(Homopiperidin-1-yl)-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine

5                   Following the procedures described in Example 1, Step 5, but substituting homopiperidine for pyrrolidine, the title compound was obtained as a solid, m.p. 161.4-163.5°C.

## EXAMPLE 7

10

3-(4-Methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine

15           Step 1:     2-Chloro-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine

To a solution of 2-amino-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (1.2 g) in water/concentrated HCl (9.5 mL:1 mL) at 0°C was added a solution of sodium nitrite (262 mg) in 5 mL water. The mixture was warmed to r.t. and stirred overnight. An additional 30 mg of sodium nitrite was added and after 3 h the heterogeneous mixture was filtered. A portion of the solid (250 mg) and POCl<sub>3</sub> (110 mL) in DMF (2 mL) was heated at 70°C for 60 h. The mixture was cooled to r.t., diluted with water and extracted with ethyl acetate. The organics were washed with brine, dried and concentrated to provide the title compound as a pale yellow solid (270 mg) that was used as such in the subsequent reaction.

30           Step 2:     3-(4-Methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine

A mixture of (S)-2-pyrrolidinemethanol (400 mg), cesium carbonate (1 g) and 2-chloro-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (600 mg) in DMF (6 mL) was stirred at 80°C until tlc analysis indicated completion of the reaction (15 h). Water was added and the mixture was extracted with ether. The organics were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. Flash

chromatography (3:7 hexane/ethyl acetate) provided the title compound as a white foam (470 mg).

Elemental Analysis:      Calculated: C, 53.99;    H, 4.78;    N, 7.00  
                                 Found:      C, 54.13;    H, 4.93;    N, 6.89

5

## EXAMPLE 8

3-(4-Methylsulfonyl)phenyl-2-((2R)-2-hydroxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine

10            Following the procedures described in Example 7, Step 2, but substituting (R)-2-pyrrolidinemethanol for (S)-2-pyrrolidinemethanol, the title compound was obtained as a white foam.

Elemental Analysis:      Calculated: C, 53.99;    H, 4.78;    N, 7.00  
                                 Found:      C, 53.75;    H, 4.76;    N, 6.78

15

## EXAMPLE 9

5-Chloro-3-(4-methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-ylpyridine

20            A mixture of (S)-2-pyrrolidinemethanol (2 mL), CuI (16 mg) and 2,5-dichloro-3-(4-methylsulfonyl)phenylpyridine (510 mg) was stirred at 100°C until tlc analysis indicated completion of the reaction (15 h). Water was added and the mixture was extracted with ether. The organics were washed with brine, dried (MgSO<sub>4</sub>) and concentrated.

25            Flash chromatography (3:7 hexane/ethyl acetate) provided the title compound as a white foam (500 mg).

Elemental Analysis:      Calculated: C, 55.66;    H, 5.22;    N, 7.64  
                                 Found:      C, 55.68;    H, 5.32;    N, 7.47

30

## EXAMPLE 10

3-(4-Methylsulfonyl)phenyl-2-((2S)-2-methoxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine

Following the procedures described in Example 7, Step 2, but substituting (S)-2-(methoxymethyl)pyrrolidine for (S)-2-pyrrolidinemethanol, the title compound was obtained as a white foam.

Elemental Analysis:      Calculated: C, 55.06;    H, 5.11;    N, 6.76  
5                              Found:        C, 55.24;    H, 4.94;    N, 6.69

#### EXAMPLE 11

10    3-(4-Methylsulfonyl)phenyl-2-((2S)-2-acetoxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine

To a solution of 3-(4-methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine (200 mg) and DMAP (catalytic) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at r.t. was added acetic anhydride (0.1 mL). After 2 h, water was added and the mixture was extracted  
15 with ether. The organics were dried and concentrated. Flash chromatography of the residual material (3:2 hexane/ethyl acetate) provided the title compound as a white foam (160 mg).

Elemental Analysis:      Calculated: C, 54.29;    H, 4.78;    N, 6.33  
20                              Found:        C, 54.09;    H, 4.74;    N, 6.17

#### EXAMPLE 12

25    5-Chloro-3-(4-methylsulfonyl)phenyl-2-((2S)-2-methoxymethyl)pyrrolidin-1-ylpyridine

To a solution of 5-chloro-3-(4-methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-ylpyridine (65 mg) and methyl iodide (0.1 mL) in DMF (5 mL) at r.t. was added potassium *t*-butoxide (0.5 mL of a 1 M solution in THF). After 10 min, saturated ammonium chloride was added and the mixture extracted with ethyl acetate. The organics were  
30 dried and concentrated. Flash chromatography of the residue (4:1 hexane/ethyl acetate) provided the title compound as a white foam.

<sup>1</sup>H NMR (500 MHz, acetone-d<sub>6</sub>): δ 1.5-1.63 (m, 1H), 1.6-1.83 (m, 2H), 1.97-2.05 (m, 1H), 2.60 (dt, 1H), 2.85 (dt, 1H), 3.15 (s, 3H), 3.30 (s, 3H), 3.40 (dd, 1H), 3.59 (dd, 1H), 4.48 (m, 1H), 7.55 (d, 1H), 7.71 (d, 2H), 7.98 (d, 2H), 8.11  
35 (d, 1H).

### EXAMPLE 13

3-(4-Methylsulfonyl)phenyl-2-(2-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine

A mixture of 2-(hydroxymethyl)piperidine (1 mL), CuI (10 mg) and 2-chloro-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (200 mg) was stirred at 100°C for 15 h. Water was added and the mixture was extracted with ether. The organics were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (1:1 hexane/ethyl acetate) provided the title compound as a white foam (50 mg).

Elemental Analysis:	Calculated: C, 55.06;	H, 5.11;	N, 6.76
	Found: C, 54.74;	H, 5.34;	N, 6.51

### EXAMPLES 14 AND 15

(-)-3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine and (+)-3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine

**Step 1:** Racemic 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine

Following the procedures described in Example 13, but substituting 3-(hydroxymethyl)piperidine for 2-

(hydroxymethyl)piperidine, the title compound was obtained as a white solid.

<b>Elemental Analysis:</b>	<b>Calculated:</b> C, 55.06; H, 5.11; N, 6.76
	<b>Found:</b> C, 54.74; H, 5.15; N, 6.62

Step 2: (-)-3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine and (+)-3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine

A portion (100 mg) of the racemic material obtained in Step 1 was subjected to HPLC using a chiral column (chiralpak AD from

DAICEL; 2 X 25 cm) and an eluant of hexane/isopropanol (80:20) at a flow rate of 9 mL/min (10 X 10 mg injections). The first compound to be eluted (monitoring at 290 nm) with a retention time of 11.6 min was obtained as a white solid (40 mg) after concentration ( $[\alpha]_D -78^\circ$ ;  $c = 0.205$ , CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR analysis of the derived Mosher's ester indicated >98% ee. The second eluting compound (retention time 12.5 min) was obtained as a white solid (15 mg) after concentration ( $[\alpha]_D +72.2^\circ$ ;  $c = 0.18$ , CH<sub>2</sub>Cl<sub>2</sub>). <sup>1</sup>H NMR analysis of the derived Mosher's ester indicated ~98% ee.

10

## EXAMPLE 16

5-Chloro-3-(4-methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-ylpyridine

15

Following the procedures described in Example 9, but substituting 3-(hydroxymethyl)piperidine for (S)-2-pyrrolidinemethanol, the title compound was obtained as a pale yellow foam.

Elemental Analysis:      Calculated: C, 56.76;      H, 5.56;      N, 7.35  
                                 Found:      C, 52.92;      H, 5.75;      N, 7.34

20

## EXAMPLE 17

3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl-3-methyl)piperidin-1-yl-5-trifluoromethylpyridine

25

Step 1:      3-Hydroxymethyl-3-methylpiperidine

To ethyl nipecotate (1.3 g) in THF (20 mL) at r.t. was added potassium bis(trimethylsilyl)amide (18 mL of a 0.5 M solution in toluene). After 1 h, methyl iodide (0.5 mL) was added and the mixture was stirred for 15 h. Water was added and the mixture extracted with ether. The organics were washed with brine, dried and concentrated. The residual material (1.3 g) was dissolved in THF (20 mL) and treated with lithium aluminum hydride (8.7 mL of a 1 M solution in THF) at r.t. After 15 h, the mixture was cooled to -5°C and aqueous sodium

35

potassium tartrate was added followed by concentrated  $\text{NH}_4\text{OH}$ , 10 N NaOH and the resulting mixture was stirred for 30 min. The mixture was filtered through anhydrous sodium sulfate and the filtrate was concentrated from toluene twice. The residual oil (1 g), containing the title compound, was used without further purification in Step 2.

Step 2: 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl-3-methyl)piperidin-1-yl-5-trifluoromethylpyridine

A mixture of crude 3-hydroxymethyl-3-methylpiperidine from Step 1 (500 mg) and 2-chloro-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (330 mg) was stirred at  $100^\circ\text{C}$  for 3 h. Water was added and the mixture was extracted with ethyl acetate. The organics were washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography (2:3 hexane/ethyl acetate), followed by stirring the semi-purified material vigorously in ether/hexane, provided the title compound as a white solid (250 mg).

Elemental Analysis:      Calculated: C, 56.06;      H, 5.41;      N, 6.54  
                                 Found:      C, 55.83;      H, 4.70;      N, 6.42

20

## EXAMPLE 18

3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)homopiperidin-1-yl-5-trifluoromethylpyridine

25 Step 1: N-Benzyl  $\epsilon$ -caprolactam

To a solution of  $\epsilon$ -caprolactam (28.3 g) in THF (500 mL) and DMF (20 mL) at r.t. was added sodium hydride (12 g of 60% in oil) portionwise. After the addition was complete, benzyl bromide (29.7 mL) was added dropwise and upon completion, the mixture was stirred for 15 h. To the mixture was carefully added saturated ammonium chloride and the resulting mixture was extracted twice with ethyl acetate. The organics were washed with water and brine, dried and concentrated. The title compound was obtained as a white solid and used in Step 2 without further purification.

Step 2: 3-(Hydroxymethyl)homopiperidine

To a solution of LDA (prepared at 0°C from 5.3 mL of diisopropylamine and 15.8 mL of 2.4 M *n*-BuLi in hexanes) in THF (150 mL) at -78°C was added N-benzyl  $\epsilon$ -caprolactam (7 g) from Step 1. The mixture was warmed to -40°C and then cooled to -98°C. To the cold solution was added ethyl formate (5 eq) and then the mixture was warmed to r.t. Saturated ammonium chloride was added and the resulting mixture was extracted twice with ethyl acetate. The organics were washed with water and brine, and then filtered through a pad of silica gel. The filtrate was concentrated to provide the formylated product (6 g) that was used as such. The residual material was dissolved in THF (100 mL) and treated with lithium aluminum hydride (2 eq of 1 M solution in THF) at r.t. After 15 h, the mixture was cooled to -5°C and aqueous sodium potassium tartrate was added followed by concentrated NH<sub>4</sub>OH, 10 N NaOH and the resulting mixture was stirred for 30 min. The mixture was filtered through anhydrous sodium sulfate and the filtrate was then filtered through a pad of silica gel. The filtrate was concentrated to provide the reduced product (2.2 g) that was used as such. A mixture of the crude material and 10% Pd-C (200 mg) in ethanol (100 mL) was stirred under an atmosphere of hydrogen (1 atm) for 2 days. The mixture was filtered through a pad of Celite and the filtrate was concentrated. Flash chromatography of the residual material (ethyl acetate) provided the title compound as an oil that was used as such in Step 3.

Step 3: 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)homopiperidin-1-yl-5-trifluoromethylpyridine

Following the procedures described in Example 13, but substituting 3-(hydroxymethyl)homopiperidine for 2-(hydroxymethyl)piperidine, the title compound was obtained as a white solid.

Elemental Analysis:	Calculated:	C, 56.06;	H, 5.41;	N, 6.54
	Found:	C, 55.86;	H, 5.30;	N, 6.44

## EXAMPLE 19

5 3-(4-Methylsulfonyl)phenyl-2-(2-(2-hydroxyethyl))piperidin-1-yl-5-trifluoromethylpyridine

A mixture of 2-piperidineethanol (1.5 g), CuI (20 mg) and 2-chloro-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (336 mg) was stirred at 130°C for 15 h. Water was added and the mixture was  
10 extracted with ether. The organics were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (1:1 hexane/ethyl acetate) provided the title compound as a white solid (56 mg), m.p. 136-137°C.

## 15 EXAMPLES 20 AND 22

3-(4-Methylsulfonyl)phenyl-2-(4-oxo)piperidin-1-yl-5-trifluoromethylpyridine and 3-(4-Methylsulfonyl)phenyl-2-(4-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine

20 Step 1: 3-(4-Methylsulfonyl)phenyl-2-(4-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine

A mixture of 4-hydroxypiperidine (1 g), CuI (20 mg), diisopropylethylamine (1 mL) and 2-chloro-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (336 mg) was stirred at 100°C for 15 h. 1 N HCl and CH<sub>2</sub>Cl<sub>2</sub> were added and the mixture was extracted with ethyl  
25 acetate and ether. The combined organics were washed with saturated ammonia and brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (1:1 hexane/ethyl acetate) provided the title compound  
30 (Example 22) as a white solid (147 mg), m.p. 185-186.5°C.

Step 2: 3-(4-Methylsulfonyl)phenyl-2-(4-oxo)piperidin-1-yl-5-trifluoromethylpyridine

A mixture of 3-(4-methylsulfonyl)phenyl-2-(4-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine from Step 1 (400 mg),  
35



3A° molecular sieves (1 g), TPAP (catalytic) and NMO (234 mg) in acetonitrile (10 mL) was stirred for 15 h at r.t. The mixture was filtered and the filtrate was concentrated. Flash chromatography (1:1 hexane/ethyl acetate), followed by stirring the semi-purified material vigorously in ether, provided the title compound (Example 20) as a beige solid (77 mg).

Elemental Analysis:      Calculated: C, 54.27;      H, 4.30;      N, 7.03  
Found:      C, 53.98;      H, 4.23;      N, 6.91

10

## EXAMPLES 21 AND 23

3-(4-Methylsulfonyl)phenyl-2-(3-oxo)piperidin-1-yl-5-trifluoromethylpyridine and 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine

15

Step 1:      3-(4-Methylsulfonyl)phenyl-2-(3-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine

Following the procedures described in Examples 20 and 22, Step 1, but substituting 3-hydroxypiperidine for 4-hydroxypiperidine, the title compound (Example 23) was obtained as a white solid.

20

Elemental Analysis:      Calculated: C, 53.99;      H, 4.78;      N, 7.00  
Found:      C, 53.72;      H, 5.00;      N, 7.10

25

Step 2:      3-(4-Methylsulfonyl)phenyl-2-(3-oxo)piperidin-1-yl-5-trifluoromethylpyridine

Following the procedures described in Examples 20 and 22, Step 2, but substituting 3-(4-methylsulfonyl)phenyl-2-(3-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine from Step 1 for 3-(4-methylsulfonyl)phenyl-2-(4-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine, the title compound (Example 21) was obtained as a beige solid, m.p. 176-176.5°C.

30

35

## EXAMPLE 24

2-(4,4-Difluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine

A mixture of 3-(4-methylsulfonyl)phenyl-2-(4-oxo)piperidin-1-yl-5-trifluoromethylpyridine (480 mg) and DAST (0.32 mL) in benzene (12 mL) was heated at reflux for 3 h. Saturated sodium carbonate was carefully added and the mixture was extracted with ethyl acetate. The combined organics were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (3:2 hexane/ethyl acetate), followed by stirring the semi-purified material vigorously in ether, provided the title compound as a white solid (340 mg).

Elemental Analysis:      Calculated: C, 51.43;      H, 4.08;      N, 6.66  
                                 Found:      C, 51.62;      H, 3.88;      N, 6.57

EXAMPLE 25

2-(3,3-Difluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine

Following the procedures described in Examples 24, but substituting 3-(4-methylsulfonyl)phenyl-2-(3-oxo)piperidin-1-yl-5-trifluoromethylpyridine for 3-(4-methylsulfonyl)phenyl-2-(4-oxo)piperidin-1-yl-5-trifluoromethylpyridine, the title compound was obtained as an off-white solid, m.p. 152.5-153.5°C.

EXAMPLE 26

2-(4-Fluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine

To a solution of 3-(4-methylsulfonyl)phenyl-2-(4-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine (150 mg) in CH<sub>2</sub>Cl<sub>2</sub> (1.9 mL) at -78°C was added DAST (74 mL). The mixture was warmed to r.t. and then saturated sodium carbonate was carefully added. The mixture was extracted with ethyl acetate and the combined organics were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. Flash

chromatography (3:2 hexane/ethyl acetate), followed by stirring the semi-purified material vigorously in ether, provided the title compound as a white solid (115 mg), m.p. 136-137.5°C.

5

## EXAMPLE 27

3-(4-Methylsulfonyl)phenyl-2-morpholin-4-yl-5-trifluoromethylpyridine

Following the procedures described in Example 13, but substituting morpholine for 2-(hydroxymethyl)piperidine, the title compound was obtained as a white solid, m.p. 159-160°C.

10

## EXAMPLE 28

3-(4-Methylsulfonyl)phenyl-2-thiomorpholin-4-yl-5-

trifluoromethylpyridine A mixture of thiomorpholine (350 mg), CuI (20 mg), N-ethyl morpholine (2 mL) and 2-chloro-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine (500 mg) was stirred at 128°C for 15 h. 1 N HCl and CH<sub>2</sub>Cl<sub>2</sub> were added and the mixture was extracted with ethyl acetate and ether. The combined organics were washed with saturated ammonia and brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (1:1 hexane/ethyl acetate), followed by stirring the semi-purified material vigorously in ether, provided the title compound as a white solid (460 mg).

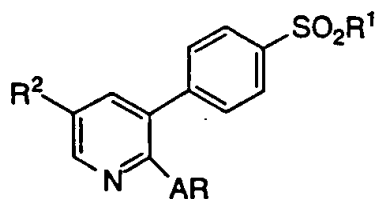
20

Elemental Analysis:      Calculated: C, 50.74;      H, 4.26;      N, 6.96  
Found:                    C, 50.56;      H, 4.34;      N, 6.90

25

## WHAT IS CLAIMED IS:

1. A compound of Formula I



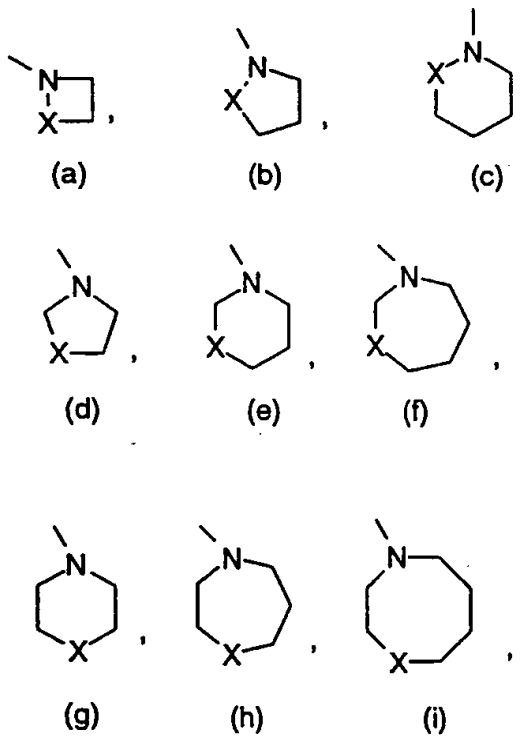
5

I

or a pharmaceutically acceptable salt thereof  
wherein:

-AR is selected from the group consisting of

10



- 15 X is selected from the group consisting of  
(a) CR<sup>3</sup>R<sup>4</sup>,

(b) O,

(c) S,

R<sup>1</sup> is selected from the group consisting of

(a) CH<sub>3</sub>,

5 (b) NH<sub>2</sub>,

(c) NHC(O)CF<sub>3</sub>,

R<sup>2</sup> is chosen from the group consisting of

(a) hydrogen

(b) C<sub>1-6</sub>alkyl

10 (c) C<sub>1-6</sub>alkoxy,

(d) C<sub>1-6</sub>alkylthio,

(e) C<sub>1-6</sub>fluoroalkyl,

(f) C<sub>1-6</sub>fluoroalkoxy,

(g) CN,

15 (h) -CO<sub>2</sub>R<sup>6</sup>,

(i) -C(R<sup>7</sup>)(R<sup>8</sup>)-OH,

(j) -C<sub>1-6</sub>alkyl-CO<sub>2</sub>-R<sup>9</sup>,

(k) halo,

(l) hydroxy,

20 (m) N<sub>3</sub>,

(n) NO<sub>2</sub>,

(o) NR<sup>10</sup>R<sup>11</sup>,

(o) NHCOR<sup>12</sup>,

R<sup>3</sup> and R<sup>4</sup> are independently chosen from the group consisting of

25 (a) hydrogen,

(b) C<sub>1-6</sub>alkyl,

(c) (CH<sub>2</sub>)<sub>p</sub>OR<sup>5</sup>,

(d) F,

or R<sup>3</sup> and R<sup>4</sup> are together O,

30 R<sup>5</sup> is selected from the group consisting of

(a) hydrogen,

(b) C<sub>1-6</sub>alkyl,

(c) C<sub>1-5</sub>acyl,

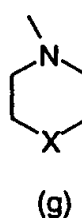
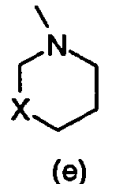
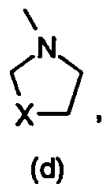
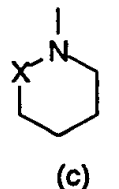
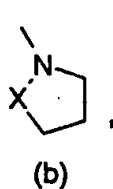
R<sup>6</sup> to R<sup>12</sup> are independently chosen from the group consisting of

35 (a) hydrogen

(b) C<sub>1-6</sub>alkyl, and

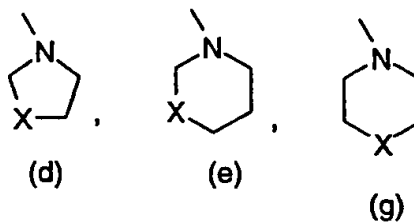
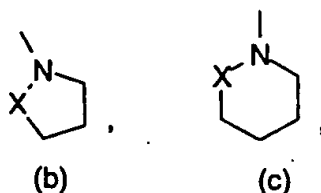
p is 0, 1, 2.

2. A compound according to Claim 1 wherein  
 $R^1$  is  $CH_3$ .
3. A compound according to Claim 1 wherein  
 $R^2$  is halo or  $C_{1-6}$ fluoroalkyl.
4. A compound according to Claim 1 wherein  
 $X$  is  $CR^3R^4$ .
5. A compound according to Claim 1 wherein  
 $R^2$  is chosen from the group consisting of
- (a) hydrogen
  - (b)  $C_{1-6}$ alkyl
  - (c)  $C_{1-6}$ alkoxy,
  - (d)  $C_{1-6}$ alkylthio,
  - (e)  $C_{1-6}$ fluoroalkyl,
  - (f) CN,
  - (g) halo,
  - (h) hydroxy.
6. A compound according to Claim 1 where Ar is  
 selected from



7. A compound according to Claim 1 wherein

-AR is selected from the group consisting of



5

X is selected from the group consisting of

(a)  $CR^3R^4$ ,

$R^1$  is selected from the group consisting of

10

(a)  $CH_3$ ,

(b)  $NH_2$ ,

$R^2$  is chosen from the group consisting of

(a) hydrogen

(b)  $C_{1-4}$ alkyl

15

(c)  $C_{1-4}$ alkoxy,

(d)  $C_{1-4}$ alkylthio,

(e)  $C_{1-4}$ fluoroalkyl,

(f)  $CN$ ,

(g) halo,

20

(h) hydroxy,

$R^3$  and  $R^4$  are independently chosen from the group consisting of

(a) hydrogen,

(b)  $C_{1-4}$ alkyl,

(c)  $(CH_2)_pOR^5$ ,

25

(d) F,

or  $R^3$  and  $R^4$  are together O,

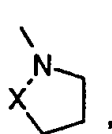
$R^5$  is selected from the group consisting of

- (a) hydrogen,
- (b) C<sub>1</sub>-6alkyl,
- (c) C<sub>1</sub>-5acyl,

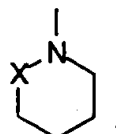
p is 0, 1, 2.

5

8. A compound according to Claim 7 wherein  
-AR is selected from the group consisting of

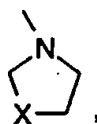


(b)

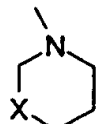


(c)

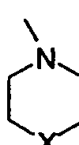
10



(d)



(e)



(g)

X is selected from the group consisting of

- (a) CR<sup>3</sup>R<sup>4</sup>,

15 R<sup>1</sup> is selected from the group consisting of

- (a) CH<sub>3</sub>,
- (b) NH<sub>2</sub>,

R<sup>2</sup> is C<sub>1</sub>-4fluoroalkyl,

R<sup>3</sup> and R<sup>4</sup> are independently chosen from the group consisting of

- 20 (a) hydrogen,
- (b) C<sub>1</sub>-3alkyl,
- (c) (CH<sub>2</sub>)<sub>p</sub>OR<sup>5</sup>,
- (d) F,

or R<sup>3</sup> and R<sup>4</sup> are together O,

25 R<sup>5</sup> is selected from the group consisting of

- (a) hydrogen,
- (b) methyl or ethyl,

p is 0 or 1.



9. A compound selected from the group consisting of
- (1) 3-(4-Methylsulfonyl)phenyl-2-pyrrolidin-1-yl-5-trifluoromethylpyridine,
  - (2) 3-(4-Methylsulfonyl)phenyl-2-piperidin-1-yl-5-trifluoromethylpyridine,
  - (3) 5-Chloro-3-(4-methylsulfonyl)phenyl-2-piperidin-1-ylpyridine,
  - (4) 3-(4-Methylsulfonyl)phenyl-2-piperidin-1-ylpyridine,
  - (5) 3-(4-Methylsulfonyl)phenyl-2-(1,2,3,6-tetrahydropyridin-1-yl)-5-trifluoromethylpyridine,
  - (6) 2-(Homopiperidin-1-yl)-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine,
  - (7) 3-(4-Methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine,
  - (8) 3-(4-Methylsulfonyl)phenyl-2-((2R)-2-hydroxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine,
  - (9) 5-Chloro-3-(4-methylsulfonyl)phenyl-2-((2S)-2-hydroxymethyl)pyrrolidin-1-ylpyridine,
  - (10) 3-(4-Methylsulfonyl)phenyl-2-((2S)-2-methoxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine,
  - (11) 3-(4-Methylsulfonyl)phenyl-2-((2S)-2-acetoxymethyl)pyrrolidin-1-yl-5-trifluoromethylpyridine,
  - (12) 5-Chloro-3-(4-methylsulfonyl)phenyl-2-((2S)-2-methoxymethyl)pyrrolidin-1-ylpyridine,
  - (13) 3-(4-Methylsulfonyl)phenyl-2-(2-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine,
  - (14) (-)-3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine,
  - (15) (+)-3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-yl-5-trifluoromethylpyridine,
  - (16) 5-Chloro-3-(4-methylsulfonyl)phenyl-2-(3-hydroxymethyl)piperidin-1-ylpyridine,
  - (17) 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl-3-methyl)piperidin-1-yl-5-trifluoromethylpyridine,

- (18) 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxymethyl)homopiperidin-1-yl-5-trifluoromethylpyridine,  
(19) 3-(4-Methylsulfonyl)phenyl-2-(2-(2-hydroxyethyl))piperidin-1-yl-5-trifluoromethylpyridine,  
5 (20) 3-(4-Methylsulfonyl)phenyl-2-(4-oxo)piperidin-1-yl-5-trifluoromethylpyridine,  
(21) 3-(4-Methylsulfonyl)phenyl-2-(3-oxo)piperidin-1-yl-5-trifluoromethylpyridine,  
(22) 3-(4-Methylsulfonyl)phenyl-2-(4-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine,  
10 (23) 3-(4-Methylsulfonyl)phenyl-2-(3-hydroxy)piperidin-1-yl-5-trifluoromethylpyridine,  
(24) 2-(4,4-Difluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine,  
15 (25) 2-(3,3-Difluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine,  
(26) 2-(4-Fluoro)piperidin-1-yl-3-(4-methylsulfonyl)phenyl-5-trifluoromethylpyridine,  
(27) 3-(4-Methylsulfonyl)phenyl-2-morpholin-4-yl-5-trifluoromethylpyridine,  
20 (28) 3-(4-Methylsulfonyl)phenyl-2-thiomorpholin-4-yl-5-trifluoromethylpyridine,

10. A pharmaceutical composition for treating an  
25 inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:  
a non-toxic therapeutically effective amount of a compound according to Claim 1, 2, 3, 4, 5, 6, 7 or 8 and a pharmaceutically acceptable carrier.  
30 11. A pharmaceutical composition for treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:  
a non-toxic therapeutically effective amount of a compound according to Claim 1, 2, 3, 4, 5, 6, 7 or 8 and a pharmaceutically acceptable  
35 carrier.

12. A method of treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent comprising:  
administration to a patient in need of such treatment of a non-toxic  
5 therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.
13. A method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively  
10 inhibits COX-2 in preference to COX-1 comprising:  
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1.
14. A pharmaceutical composition comprising a  
15 compound of Claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 and a pharmaceutically acceptable carrier.
15. Use of a compound of Claim 1, 2, 3, 4, 5, 6, 7,  
20 8 or 9 in the manufacture of a medicament for the treatment of an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

16. A compound of Claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 for use in therapy.

17. An anti-inflammatory pharmaceutical composition comprising an effective anti-inflammatory amount of a compound of Claim 9, in association with a pharmaceutically acceptable carrier.

18. A COX-2 selective, relative to COX-1, inhibitor pharmaceutical composition comprising an effective COX-2 selective inhibiting amount of a compound of Claim 9 in association with a pharmaceutically acceptable carrier.

19. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 8, for use in treating an inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

20. A compound as defined in Claim 9 for use in treating cyclooxygenase mediated diseases.

# INTERNATIONAL SEARCH REPORT

Inte: onal Application No

PCT/CA 98/00861

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/74 C07D401/04 A61K31/44 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 754 687 A (MERCK FROSST CANADA INC.) 22 January 1997 see page 16, line 18 - line 25; claims 1,27,28,30-32; tables I-IV	1,10,11, 14-20
A	WO 94 13635 A (MERCK FROSST CANADA INC.) 23 June 1994 see claims 1,12,17-20,24,26-30	1,10,11, 14-20
A	DE 44 19 247 A (MERCKLE GMBH) 7 December 1995 see page 5, line 54 - line 63; claims 1,7,8	1,10,14, 15
A	US 4 757 073 A (J. S. NEW ET AL.) 12 July 1988 see table 2, compounds 17,19,21	1
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 December 1998

Date of mailing of the international search report

21/12/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hass, C

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/00861

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 647 639 A (SANOFI ET AL.) 12 April 1995 see claim 1	1
A	EP 0 591 030 A (ELF SANOFI ET AL.) 6 April 1994 see claim 1	1
A	J. S. NEW ET AL.: JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 3, 1988, pages 618-24, XP002086706 see page 618, scheme I, compound no. 6a	1
A	V. N. CHARUSHIN ET AL.: JOURNAL OF ORGANIC CHEMISTRY, vol. 48, no. 16, 1983, pages 2667-71, XP002086707 see page 2667, scheme I, compounds 9a-c; page 2668, scheme IV, compound 15	1

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 98/00861

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12, 13  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/CA 98 00861

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 12 and 13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

-----

Claims Nos.: 12,13

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 98/00861

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 754687	A	22-01-1997	US 5474995 A	12-12-1995
			EP 0822190 A	04-02-1998
			AT 165825 T	15-05-1998
			AU 1913297 A	14-08-1997
			AU 691119 B	07-05-1998
			AU 6197096 A	31-10-1996
			AU 6967494 A	17-01-1995
			BG 100247 A	28-06-1996
			BR 9406979 A	05-03-1996
			CA 2163888 A	05-01-1995
			CA 2176973 A	25-12-1994
			CA 2176974 A	25-12-1994
			WO 9500501 A	05-01-1995
			CN 1125944 A	03-07-1996
			CZ 9503146 A	15-05-1996
			DE 69410092 D	10-06-1998
			EP 0705254 A	10-04-1996
			ES 2115237 T	16-06-1998
			FI 956119 A	19-12-1995
			HR 940373 A	31-12-1996
			HU 74070 A	28-10-1996
			JP 9500372 T	14-01-1997
			MX 9404749 A	31-01-1995
			NO 955256 A	23-02-1996
			NZ 267386 A	26-02-1998
			PL 312196 A	01-04-1996
			SG 52703 A	28-09-1998
			SK 150295 A	08-01-1995
			US 5536752 A	16-07-1996
			US 5550142 A	27-08-1996
			US 5710140 A	20-01-1998
			US 5840746 A	24-11-1998
			ZA 9404501 A	13-03-1995
			AU 1269495 A	01-08-1995
			BG 100350 A	31-12-1996
			BR 9408478 A	26-08-1997
			CA 2180651 A	13-07-1995
			WO 9518799 A	13-07-1995
			CN 1143365 A	19-02-1997
			EP 0739340 A	30-10-1996
			FI 962800 A	06-09-1996
			HU 74986 A	28-03-1997
			JP 2788677 B	20-08-1998
			JP 9506631 T	30-06-1997
			NO 960393 A	09-07-1996
			SG 43841 A	14-11-1997
WO 9413635	A	23-06-1994	US 5604260 A	18-02-1997
			AU 5621594 A	04-07-1994
			CA 2151235 A	23-06-1994
			DE 69321604 D	19-11-1998
			EP 0673366 A	27-09-1995
			JP 8504408 T	14-05-1997
DE 4419247	A	07-12-1995	US 5840746 A	24-11-1998
			AU 2673095 A	21-12-1995
			CA 2191746 A	07-12-1995
			WO 9532972 A	07-12-1995

# INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. Appl. Application No.

PCT/CA 98/00861

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4419247 A		EP 0763037 A FI 964773 A JP 10506370 T NO 965095 A	19-03-1997 27-01-1997 23-06-1998 29-11-1996
US 4757073 A	12-07-1988	NONE	
EP 647639 A	12-04-1995	AU 6488198 A AU 687090 B AU 7574594 A CA 2133855 A CN 1106400 A FI 944751 A HU 71349 A JP 7165754 A NO 943826 A NZ 264634 A SG 47476 A US 5502063 A US 5595994 A US 5723611 A ZA 9407924 A	02-07-1998 19-02-1998 27-04-1995 12-04-1995 09-08-1995 12-04-1995 28-11-1995 27-06-1995 12-04-1995 21-12-1995 17-04-1998 26-03-1996 21-01-1997 03-03-1998 26-05-1995
EP 591030 A	06-04-1994	AU 661198 B AU 4756693 A CA 2106840 A HU 65405 A JP 6192251 A MX 9305910 A US 5410057 A US 5565474 A US 5576320 A	13-07-1995 31-03-1994 26-03-1994 28-06-1994 12-07-1994 31-05-1994 25-04-1995 15-10-1996 19-11-1996